FOR PRIVATE CIRCULATION

For the use of Registered
Medical Practitioners only

QUARTERLY MEDICAL REVIEW

Vol. 47, No. 2 **Apr., 1996**

CONTENTS

Review : **IRON DEFICIENCY AND IRON OVERLOAD SYNDROME**

Iron Deficiency Anaemia..... 1
Non haematological effects of Iron Deficiency..... 16
Iron Overload Syndrome..... 18
References..... 29

Published and issued by
RAPTAKOS, BRETT & CO. LTD., WORLI, MUMBAI 400 025.

Introducing...

New Siderfol

The ladies special haematinic with six vital hemopoietic factors.

- Iron
- Folic acid
- Vitamin B_{12}
- Vitamin C
- Vitamin B_6
- Copper

Siderfol

The ladies special haematinic

QUARTERLY
MEDICAL REVIEW

Vol. 47, No. 2 Apr., 1996

IRON DEFICIENCY AND IRON OVERLOAD SYNDROME

DR. M.B. AGARWAL*

Iron deficiency is probably the commonest disorder seen in man, affecting over half of mankind. Although considered rare, iron overload is slowly being considered as an important cause of preventable morbidity and mortality. In this presentation, we would review these two disorders of iron metabolism.

IRON DEFICIENCY ANAEMIA

Iron deficiency is the commonest cause of anaemia[1]. It is also the commonest nutritional disorder in humans. Although more common in the developing countries, it is widely prevalent almost all over the world. The exact prevalence of iron deficiency anaemia is difficult to define[1].

Iron Balance [2] :

The full term infant has approximately 250 mg of iron at birth (80 mg iron/kg). About 100 mg (0.3 mg/day) of iron is required in the first year to maintain the haemoglobin at normal level (11 g/dl). As against this, the premature infant has only about 160 mg of iron at birth and hence requires 300 mg (1 mg/day) of iron during the first year[2]. From the age of two years until adolescence, the daily iron requirement increases by 0.5 to 1.0 mg/day[2]. This is because of three factors :

(a) growth
(b) increased iron losses (0.2 - 0.5 mg/day)
(c) higher normal haemoglobin level

During adolescence, daily iron requirement increases to 1.6 mg for males.

* ***Hon. Haematologist,*** *Bombay Hospital P G Institute of Medical Sciences, Marine Lines, Bombay 400 020.*
Hon. Assoc.Physician & Haematologist, *LTMG Hospital & Medical College, Sion, Bombay 400 022.*

Subsequently, the requirement drops to 1.0-1.2 mg/day as approximately 1.0 mg/day of iron is lost in adult man. This includes - 0.6 mg in faeces, 0.3 mg from skin, and 0.1 mg in urine[3]. The menstruating woman loses 30 ml of blood per month and therefore her iron requirements increase by 0.5 mg/day[2]. Lastly, during pregnancy, daily iron requirement is 0.8, 4.0 and 6.0 mg/day during first, second, and third trimester respectively. This is because 1.2 gm of iron is needed during pregnancy to supply the requirements to the foetus, to take care of blood loss during delivery and also for the expansion of the red cell mass. The net loss however is 750 mg only as the remaining 450 mg meant for increase in red cell mass, is once again available to the body after delivery.

Aetiology of Iron Deficiency :

Deficient intake, poor bioavailability, malabsorption and bleeding should take care of most of the known causes of iron deficiency.

The important factors deciding iron absorption are[3,4] :
1) The amount of iron ingested
2) Its bio-availability
3) Iron status of the patient

Absorption is controlled primarily by the mucosal cells of the proximal small intestine. The iron absorbed is inversely proportional to the amount of iron present in the body stores. In addition, ineffective erythropoiesis promotes iron absorption[2]. Thus iron deficiency could occur, if dietary intake of bioavailable iron is inadequate, absorption is impaired, or if bleeding occurs.

Intake of Bioavailable iron [5-10] :

Average daily diet contains much more iron than what the body requires. Therefore, nutritional iron deficiency is actually the result of poor iron-bioavailability. Different sources of food iron have different bio- availability. Also, there are many enhancers and inhibitors for iron absorption and hence, bioavailability of iron is the characteristic of overall meal composition rather than a specific item. The heme iron which is a part of haemoglobin and myoglobin from meat is almost always readily absorbed. All other iron (termed as non-heme iron) forms a large pool, but its bioavailability is markedly affected by other dietary items. Table I gives a list of food components (enhancers or inhibitors) that affect dietary non-heme iron bioavailability.

Thus, the two significant enhancers are ascorbic acid and animal tissue. These can increase iron absorption by 2-4 fold. This applies to most animal products except milk, eggs and cheese. The potent inhibitors include tannic acid (present in tea), polyphenolic compound (present in Coffee), white or yolk of eggs (which contain vitalin) and wheat bran. These food items consistently decrease iron absorption. Many cereals and vegetables also inhibit iron absorption as they contain tannic acid. The fibre present in vegetable

food and bran is also an inhibitor. Soya products used as protein source in food supplement also inhibit iron absorption. Lastly inorganic calcium, phosphate salts and EDTA also reduce iron availability.

Unfortunately, the enhancers i.e. animal tissue and ascorbic acid are not easily available to the people in the developing world while the inhibitors are present in large amount. This results in very high incidence of iron deficiency in the developing world.

TABLE I : FOOD COMPONENTS THAT AFFECT DIETARY IRON BIOAVAILABILITY OF NON-HEME IRON [5-10]

A.	**Enhancers**
	Ascorbic acid
	Animal tissue (meat and fish)[6]
B.	**Inhibitors**
	Tea / Coffee[7,8]
	Eggs (Yolk and white)
	Wheat bran Fiber
	Food phytates
	Soya products[10]
	Calcium / phosphate salts
	EDTA

Mal-absorption [11-15] :

Table II enlists common causes of malabsorption of iron.

TABLE II : IRON MALABSORPTION : COMMON CAUSES [11-15]

1. Upper intestinal diseases
2. Atrophic gastritis
3. Gastrectomy
4. Gastro-jejunostomy
5. Pica - eating
6. Drugs e.g. antacid, cimetidine, tetracycline

Although rare in the Western world, the disorders affecting upper small bowel (the site for iron absorption) are common in the Indian sub-continent. This affects the iron absorption from non-heme source and acts as a major factor in the genesis of iron-deficiency anaemia. Similarly, gastric surgery is an important cause of iron deficiency while gastro-jejunostomy results in diversion of gastric content away from the area of maximal iron absorption (i.e. the duodenum). In addition, many such patients develop

ulcers at the anastamotic site and bleeding from them contributes to anaemia. The cause and effect between iron deficiency and atrophic gastritis is not very clear. Iron therapy improves the gastric mucosa and inturn, its own absorption. Pica (eating of non-food material e.g. clay) which is common in iron deficiency anaemia, may, inhibit iron absorption[12]. Many drugs e.g. antacids, tetracycline, cimetidine can inhibit iron absorption[13, 14, 15].

Iron loss [16-20] *:*

Increased menstrual loss and gastrointestinal bleeding are the commonest reasons for iron deficiency anaemia due to bleeding. Hook worm load (over 5000 ova/g of faeces) almost always leads to anaemia[16]. Less definite evidence is available for trichuriasis[17] and Schistosomiasis[18]. The common causes of GI tract bleeding in adults include peptic ulcer disease, gastritis, hiatal hernia, neoplasms and drugs (anti- inflammatory drugs, corticosteroids, anticoagulants, aminophylline) and alcohol[19]. Infants may bleed due to a thermolabile factor in cow's milk[20]. Regular blood donation, specially in females from poor communities can lead to iron deficiency.

Approach to the patient of iron deficiency :

Like any other disease, a detailed history, physical examination and certain investigations are essential in confirmir g that anaemia is due to iron deficiency and also to determine its severity and cause.

History :

It is important to remember that iron deficiency anaemia is not a complete diagnosis but often, just a manifestation of a more serious underlying disease. This is especially true for adult males and elderly people. Patient's age, sex, ethnic and racial background, occupation, menstrual history and many other details in the history serve to guide the search for an underlying cause for iron deficiency. One should consider all the conditions where blood is chronically lost from the body.

In paediatric practice, children with history of prematurity, low birth weight, twins and infants who are excessively breast or bottle fed for over a year, are all at risk of developing iron deficiency[21-27]. Table III enlists various risk factors for iron deficiency. In India, dietary factors, poor bioavailability and parasitic infestation[28] are the most important causes of iron deficiency.

Development of symptoms usually correlates with the rate with which anaemia evolves, the severity of anaemia and the nature of underlying disease. Insidious onset of iron deficiency anaemia is usually asymptomatic even with very low haemoglobin levels. Occasionally pica (vide supra) and upper oesophageal dysphagia

occur and they suggest iron deficiency. Details of gastro-intestinal surgery, if any, must be obtained[29]. The extent of gastrectomy must be carefully looked into. Similarly, excessive resection of small bowel with short bowel syndrome can result in iron deficiency[29]. Intravenous hyper-alimentation with poor copper supplement can lead to iron deficiency as copper is required for both absorption and utilisation of iron[30,31]. Since copper absorption occurs primarily in the duodenum, resection of duodenum may lead to hypocupraemia and subsequently iron deficiency[32]. Family history may suggest disorders like hereditary haemorrhagic telangiectasia, inherited coagulopathy or colonic malignancies associated with familial polyposis. Presence of thalassaemia in other members could be also helpful in eliminating elaborate laboratory investigations.

TABLE III : RISK FACTORS FOR IRON DEFICIENCY

I.	prematurity twins early ligation of cord breast fed and bottle fed infants
II.	adolescents (growth spurt)
III.	menstruating women pregnancy, lactation
IV.	parasitic infestation malnutrition gastrointestinal disease alcoholism surgery (upper G.I. tract)
V.	Bleeding G.I. tract uterus lung (rare) haematuria (rare)

Dietary history is helpful in various ways. Bioavailability of iron is poor from vegetarian diet. Maternal iron deficiency, prolonged breast feeding or even bottle feeding without iron fortified milk could contribute to iron deficiency. Food fadism may result in nutritional iron deficiency specially in adolescent age group and those consuming tea with vegetarian diet. Zinc deficiency and vitamin-A deficiency also predispose to iron deficiency. Multiple nutritional deficiencies are common in alcoholics while smoking is also a risk factor for peptic ulcer disease and malignancy.

A detailed history of medication is useful e.g. use of aspirin and other NSAIDs could lead to gastrointestinal haemorrhage while various drugs taken for peptic ulcer disease may limit iron absorption. A summary of various medications which can lead to iron deficiency through gastro-intestinal mucosal ulceration or altered haemostasis is depicted in Table IV.

TABLE IV : MEDICATIONS LEADING TO IRON DEFICIENCY ANAEMIA

A GASTROINTESTINAL MUCOSAL ULCERATION	B ALTERED HAEMOSTASIS
Acetylsalicylic acid	Warfarin
Other non steroidal anti-inflammatory drugs (NSAIDS)	Heparin
Glucocorticoids	Acetylsalicylic acid
Potassium chloride	Dipyridamole
Ethacrynic acid	Sulfinpyrazone
Ascorbic acid	Nonsteroidal anti-inflammatory drugs
	Dextrans

In menstruating women, excessive vaginal bleeding may be the sole cause for chronic or recurrent iron deficiency anaemia. Multiple pregnancies may also result in anaemia of iron deficiency. Rarely massive haematuria, haemoglobinuria and even haemosiderinuria could lead to iron deficiency.

Patients with significant iron deficiency anaemia complain of effort intolerance, various cardiorespiratory, musculoskeletal and neurological symptoms which all subside with improvement in haemoglobin and/or iron status.

Physical Examination :

Physical examination in a patient with iron deficiency anaemia involves many aspects. Significant anaemia would lead to pallor of skin, mucous membranes and palmar creases. The degree of pallor usually corellates with the severity of anaemia. Below haemoglobin level of 8 g/dl, colour of the palmar creases becomes as pale as the surrounding skin. Koilonychia (concave nail beds) strongly suggest iron deficiency.

Glossitis, angular stomatitis and atrophy of the lingual papillae may be obvious. Occasionaly retinal haemorrhage may occur specially in acute severe iron deficiency.

Cardio-pulmonary findings result primarily due to severity of anaemia rather than its aetiology. Rarely idiopathic pulmonary haemosiderosis is suggested by finding of tachypnoea, pulmonary rales and diminishing breath sounds.

Examination of the abdomen is crucial as it gives clue to the aetiology of iron deficiency anaemia (vide supra).

Laboratory evaluation :

The investigations include laboratory tests which give an idea about the presence of anaemia, its subtype (normocytic, microcytic or macrocytic), confirmation of iron deficiency as the cause of anaemia and lastly its aetiology. Confirming presence of anaemia is merely like establishing presence of fever, pain or hypertension. Further laboratory investigations are always needed to have a precise aetiology. These details are shown in Table V.

TABLE V : LABORATORY EVALUATION OF A CASE OF ANAEMIA

A. Complete blood counts including
   a) RBC indices
   b) RBC morphology
   c) Red cell distribution width

   Reticulocyte count
   Serum iron
   Serum transferrin (total iron binding capacity)
   S. ferritin
   Free erythrocyte protoporphyrin
   Bone marrow - iron staining

B. After diagnosis of iron deficiency,
   Reevaluate clinical data and investigate to know the cause :

   a) Inadequate intake
   b) Malnutrition
   c) Malabsorption

(Contd.)

(TABLE V *Contd.)*

d) Excessive loss
i) Surgical loss
ii) Gastrointestinal disease
iii) Traumatic loss
ix) Menstrual loss
Patient may need
1) Stool examination for occult blood & if positive,
2) evaluation of G.I. tract
3) evaluation of menorrhagia, if any

Complete blood counts first include estimation of haemoglobin, haematocrit and RBC count. All these give an idea about the presence of anaemia and its severity. Out of these, haemoglobin is the most trusted test and widely available. However, it must be carried out by authentic methods using proper standardisation.

Other components of complete blood counts include RBC indices (MCV, MCH, MCHC), RBC morphology, reticulocyte count and RDW (Red Cell Distribution Width). It is unfortunate that this data which forms the basis of further evaluation, is often not available. Once anaemia is confirmed to be of microcytic type (MCV < 80 fl) certain disorders have to be thought of as enlisted in Table VI. Out of this, severe microcytosis i.e. MCV below 65 fl is seen only in iron deficiency and thalassaemia[33-36]. Other conditions like sideroblastic anaemia, anaemia of chronic disease, lead intoxication and copper deficiency do not produce severe drop in MCV.

TABLE VI : DIFFERENTIAL DIAGNOSIS OF MICROCYTIC ANEMIA

Iron deficiency
Thalassemia
Sideroblastic anemia
Anaemia of chronic disease
Haemoglobinopathy (H or E)
Lead poisoning
Copper deficiency

RDW, RBC count and RBC morphology are of immense help in differentiating red cell deficiency from thalassaemia trait. For example, RDW is typically increased in iron deficiency while it is normal in thalassaemia[37-40]. RBC count is typically decreased in iron deficiency whereas an erythrocytosis accompanies the thalassaemias. Punctate stippling and presence of large number of target cells together with anisocytosis and poikilocytosis are all suggestive of thalassaemia. Although similiar changes of a minor degree can occur in iron deficiency, punctate stippling is very unusual.

Estimation of serum iron (SI), total iron binding capacity (TIBC), S.ferritin [41-46], free erythrocyte protoporphyrin[47] and marrow examination with iron stain[48] are useful in confirming iron deficiency and also assessing its severity (Table VII). One must realise that many clinical situations may render results of iron studies misleading as depicted in Table VIII[49]. Various newer techniques of micro-computer analysis evaluate a variety of numerical discriminants obtained by automated blood analysers and these may be useful in differentiating iron deficiency from thalassaemia and anaemia of chronic diseases.

TABLE VII : HAEMATOLOGIC PARAMETERS IN IRON DEFICIENCY

Tests	**Iron deficiency anaemia**	**Normal values**
Serum iron	<35 ug/dl	65-165 ug/dl
Transferrin saturation	<16%	20-50%
Serum ferritin	<12 ug/litre	15-220 ug/l
Red cell mean corpuscular volume	<75 fl	83-97 fl
Free erythrocyte proto-porphyrin	>10 ug/dl	1-10 ug/dl
Stainable marrow iron	Absent	Present

Physiological consequences of iron deficiency develop in a sequential way. The whole process can be split into four phases (to some extent artificially) as depicted in Table IX. Thus one finds that to begin with, iron stores are depleted as seen by decreased or absent marrow stainable iron as well as decreased S. ferritin. At the same time, S.transferrin starts rising which is reflected as "increased total iron binding capacity". The second phase manifests by changes in RBC indices (decreased MCV, decreased MCH), elevated free erythrocyte protoporphyrin and decreased transferrin saturation and in the third phase, haemoglobin and haematocrit decline while at the end i.e. in the fourth phase, tissue hypoxia develops which

results in development of clinical symptoms and signs which have been discussed earlier[50, 51]

TABLE VIII : FACTORS INFLUENCING SERUM IRON STUDIES [49]

Increased serum iron
Premenstrual state
Iron ingestion
Pregnancy
Progesterone
Oral contraceptives
Iron injections
Hepatitis
Haemochromatosis
Decreased serum iron
Diurnal variation
Menstruation
Inflammation
Infection
Malignancy
Increased total iron-binding capacity
Progesterone
Oral contraceptives
Increased transferrin saturation
Iron supplements
Progesterone
Oral contraceptives
Iron injections
Haemochromatosis
Decreased transferrin saturation
Infection
Inflammation
Malignancy

TABLE IX : SEQUENTIAL PHASES OF IRON DEFICIENCY

1.	Decrease in storage iron
	Decreased tissue iron
	Decreased marrow iron
	Decreased serum ferritin
	Increased serum transferrin
2.	Decrease in iron for erythropoiesis
	Decreased MCV
	Decreased MCH
	Decreased transferrin saturation
	İncreased erythrocyte protoporphyrin
3.	Decrease in peripheral blood hemoglobin
	Decreased haemoglobin
	Decreased hematocrit
4.	Decrease in tissue oxygen delivery
	Clinical symptoms
	Clinical signs

Reticulocyte count is an extremely useful test but unfortunately neglected. Reticulocyte is a window of the marrow. It is best to calculate the reticulocyte index which accounts for the degree of anaemia and the longer life span of reticulocytes. Calculation of reticulocyte index is shown in Table X. In iron deficiency anaemia, the reticulocyte count and more significantly the reticulocyte index is normal.

TABLE X : THE RETICULOCYTE INDEX

$$\text{Reticulocyte index} = \frac{\text{Reticulocyte count}}{\text{Maturation index}}$$

$$\text{Maturation index} = \frac{\text{Measured hematocrit}}{\text{Normal hematocrit}}$$

Measured hematocrit	Maturation index
45	1.0
35	1.5
25	2.0
15	2.5

Table XI gives the differential laboratory findings in the four relatively common microcytic anaemias. Total iron binding capacity is increased in iron deficiency anaemia only and hence it is a pathognomonic finding in iron deficiency . In chronic diseases, it decreases while in remaining conditions, it is usually normal. In a typical iron deficiency anaemia serum iron is below 35 ug/dl[52], TIBC is over 350 ug/dl and transferr in saturation is below 16%[53]. TIBC below 250 ug is unusual in iron deficiency and the same applies to transferrin saturation above 20%[54]. Similarly serum iron below 10 ug% does not occur in conditions other than iron deficiency [52].

TABLE XI : DIFFERENTIAL LABORATORY FINDINGS IN MICROCYTIC ANAEMIAS

	Iron defi-ciency	Anaemia of chronic disease	Thal. synd romes	Sidero blastic anaemias
MCV	Low	Low or normal	very low	Low, normal or high
Serum iron	Low	Low	Normal	Normal
Total iron-binding capacity	High	Low	Normal	Normal
% saturation	Low	Low	Normal	Normal
Ferritin	Low	High	Normal	Normal
Free erythrocyte protoporphyrin	High	Normal	Normal	Normal
Red-cell count	Low	Low	High	Low
RDW	High	Normal	Normal	High

S.ferritin provides the non-invasive measurement of the total iron body stores[55]. It normally ranges from 12-220 ng/ml and the only condition in which it is decreased is iron deficiency. Although less sensitive, it is very specific as no other disease including anaemia of chronic disorders reduces S.ferritin. It can predict 90% of cases of iron deficiency in comparison with bone marrow evaluation[55, 56].

Free erythrocyte protoporphyrin although not widely available, is an additional useful test[57, 58]. Unfortunately, it cannot be considered as a very sensitive test as it can miss mild iron deficiency. Also besides iron deficiency, free erythrocyte protoporphyrin is increased in all the conditions where there is limitation in the supply of iron to red cells. A classical example is lead poisoning[59]. On the other hand, free erythrocyte protoporphyrin can distinguish iron deficiency

from alpha thalassaemia trait as its level is normal in alpha thalassaemia.

Occasionally presence of iron deficiency in a patient who has infection, chronic inflammation, neoplasms or liver disease in addition, can only be ascertained by bone marrow iron staining[60, 61]. Even here, certain pitfalls exist. e.g. :

(1) presence of adequate marrow iron with recent massive haemorrhage.

(2) reappearence of marrow iron with parenteral iron therapy despite continued iron deficiency.

(3) Inadequate marrow specimen so as to assess stainable iron adequately.

Management :

Overt anaemia is the end point in the spectrum of iron deficiency which ranges from storage iron depletion to severe anaemia with cardiac failure. One also has to remember that besides formation of haemoglobin, iron is also required for formation of myoglobin in muscles and in minute quantities for optimum function of iron containing enzymes in various body tissues[62]. Management of iron deficiency anaemia involves iron replacement, correction of the underline defect (if present), dietary advice and occasionally transfusion support. The details of iron replacement therapy are discussed below.

Iron replacement therapy :

In majority of patients, iron can be replaced by oral route. Occasionally parenteral therapy is required.

ORAL IRON THERAPY [63] :

In majority of adults, 150 mg of elemental iron/day in divided doses is all that is required. In children, one gives 4 mg of elemental iron/kg/day. The nature of iron preparation is relatively unimportant provided its iron content is in the reduced form. Thus the only important consideration is the quantity of elemental iron in each tablet/ capsule or syrup. Ferrous sulphate is the most widely prescribed oral iron. However any other compound should be equally effective. There are various claims to promote the products on the basis of either superior absorption or reduced gastro-intestinal side effects, but there is little convincing evidence to support such therapeutic advantages between various compounds. Iron absorption is maximum when it is ingested separately from meals. However, gastro-intestinal side effects are also much more. Hence, it is advisable to take an extra amount of iron after the meals two or three times a day. Increased frequency of administration helps in decreasing the amount of iron per dose. An additional dose may be taken at bed time. Iron absorption is proportional to the degree of iron

deficiency and hence it decreases as the deficiency is corrected.

Adverse effects may be so severe that a patient is unable to take iron adequately. Under these circumstances, sustained release preparations could be used and such products are increasingly promoted by many pharmaceutical firms. Such preparations have less side effects because iron is released in a delayed fashion and invariably beyond the area of maximal iron assimilation in the upper small intestine. Thus the decreased adverse effects are invariably associated with reduction in absorption. Such preparations, hence, are only to be used for patients who are totally intolerant to the conventional forms. Recently, a novel approach (gastric delivery system - GDS)has been used to delay the release of iron within the gastro-intestinal tract[64]. Here, ferrous sulphate is enclosed in a gelatin capsule having material that becomes buoyant on exposure to gastric secretion and therefore retained in the stomach for long period. While the preparation floats on the gastric secretions, the iron is slowly released from the hydrated boundary layer. This provides a slow continuous release of iron. There are two advantages :

(1) Food inhibits iron absorption. In GDS, the bulk of meal leaves the stomach before any significant release of iron from the GDS. Thus the iron absorption may be increased to three fold.

(2) The side effects are virtually eliminated and the drug has to be taken less frequently.

Response to the therapy :

It takes 7 to 10 days of therapy to achieve the maximum reticulocyte response. The count doubles or triples over the basal level, although the degree of reticulocytosis is never dramatic. The initial rise in haemoglobin depends upon the severity of anaemia. The more severe the anaemia, the higher is the rise in haemoglobin level. It takes about eight weeks for haemoglobin to normalise, irrespective of the starting level of haemoglobin.

There are various causes of failure to obtain the complete response :

(1) Poor compliance : many patients believe that iron content of iron rich diet and various vitamin supplements are adequate for treating iron deficiency anaemia. Such patients need to be told about the need of regular intake of iron tablets.

(2) Continuing blood loss - this is often a common cause for inadequate response. Presence of occult blood in the faeces or menorrhagia are the underlying problems. Aetiologies of these need to be detected and treated.

(3) An error in the diagnosis: This is not uncommon. Thalassaemia minor and anaemia of chronic diseases are often mistaken for iron deficiency.

(4) Inadequate absorption - this is an extremely uncommon cause of therapeutic failure. Occasionally, gastrectomy, extensive resection of upper small intestine, diseased upper intestine due to disorders like celiac disease can lead to inadequate iron absorption. Duration of iron therapy is also important and one needs to take oral iron for a period of six months to replenish the depleted iron stores.

PARENTERAL IRON THERAPY [62, 65] :

Number of carefully planned scientific studies have established that recovery in Hb with parenteral iron is not faster than that with an optimal regimen of oral iron. In addition, parenteral iron often causes serious morbidity and occasional fatal anaphylactic reaction. It is more expensive as well as it requires careful supervision. Hence, it should never be undertaken just to achieve a dramatic response.

The three common indications for parenteral iron therapy are:
(1) Intractable gastro-intestinal side effects
(2) Malabsorption
(3) Severe recurrent iron deficiency due to uncontrollable blood loss.

However, the commonest practical indication is inability or unwillingness on the part of the patient to continue oral iron therapy due to persistent side effects.

Amongst various prepartions used for parenteral therapy is iron dextran which is a complex of ferric hydroxide and dextran with a molecular weight between 5000-8000. It is a dark colloidal solution containing 50 mg of elemental iron per ml. The drug is given either intra-muscularly or intra-venously. Intra-muscular injections are given in upper and outer buttock using Z-track technique to prevent skin staining. Local pain persistent for many days is common and may be due to immunological reactions to the dextran moiety. Rarely, extensive local muscle necrosis can occur. Sarcomas have been described in rats but remain undescribed in human beings.

All these problems are avoidable by giving the drug intravenously [65]. Although intial trials included intravenous administration over 10 minutes or so, a less hazardous approach is to adminster the total calculated dose in a slow and single intravenous infusion. The infusion must take 2-3 hours and the concentration of iron dextran in normal saline should not exceed 5%. The dose of iron to be administered can be calculated from the following formula :

0.3 x body weight (in pounds) X % deficiency of Hb (taking 14.5 g/dl as 100%).

This gives an amount of elemental iron required in mg% and it includes iron needed for replenshing the depleted stores. However, fatal anaphylactic reaction can still occur. Variety of other less serious side effects occur in one third of patients and these include: fever, arthralgia, skin rashes, arthritis and lymphadenopathy.

Iron dextran requires macrophage processing before the iron is released to bind transferrin. Same amount of iron gets diverted to an insoluble sequestered form. This undergoes slow mobilisation as and when iron deficiency recurs.

NON HAEMATOLOGICAL EFFECTS OF IRON DEFICIENCY

Iron is an important component of biological importance for many metabolic activities. Besides haemoglobin and myoglobin, it is intimately concerned with functioning of enzymes required for mitochondrial electron transport, DNA synthesis, detoxification mechanisms, catecholamine metabolism and a wide variety of other functions. Many non-erythroid tissue abnormalities have been described both in iron deficiency patients and in experimental animals and it has been suggested that these result from the defective synthesis of tissue iron enzymes. The total iron content of these tissue compounds is probably not more than 550 mg in an adult male.

Some of these metabolic processes involve enzymes containing iron while others require iron as a co-factor. In all animal cells, mitochondria contain an electron transport pathway which allows the evenutal oxidation of intra cellular substrates by molecular oxygen, with the generation of ATP. These pathways contain a variety of iron components which transmit electrons by means of reversible valency changes in their iron atoms. Failure of this system due to lack of oxygen supply, energy depletion or metabolic inhibitors leads to failure of energy production, accumulation of metabolities and eventual death.

The cytochromes are compounds with a single polypeptide chain. Cytochrome oxidase, which is a terminal component of the respiratory chain, contains heme group. Other components of the chain include succinate dehydrogenase, iron flavoprotein, and other non-heme-iron compounds. There is evidence that iron is also necessary for mitochondrial protein synthesis through a mechanism independent of heme synthesis and this may be important in maintaining the integrity of the organelle. Cytochrome P-450 is found in endoplasmic reticulum and plays a major part in the hydroxylation reactions associated with drug detoxification by the liver. Synthesis of intestinal mucosal cytochrome P-450 is also dependent on the iron supply from the gut lumen. Iron is also important for cell division and is required for DNA synthesis. This is probably through the iron dependence of the rate limiting enzyme ribonucleotide reductase. In red cells, globin chain synthesis is also dependent on iron. In other cells too, various processes are iron dependent, for example the enzymes tyrosine hydroxylase, phenyl-alanine hydroxylase, monoamine oxidase, proline hydroxylase and aconitase.

Iron deficiency leads to reduced myoglobin content of skeletal and heart muscle. It also leads to reduced cytochrome-C content of skeletal muscle. The same has been noted in intestinal mucosal cell. Brain cytochromes have also found to be decreased. Deficiency of catalase and perodixase have been noted. Similarly abnormal activity of mono-aminoxidase is noted.

Ensure Adequate Calcium Supplementation in Adolescence and Pregnancy / Lactation with...

Calcinol

SYURP TABLETS

Calcinol - The Calcium Supplement of choice.

In Chronic Constipation, Help patients evacuate effortlessly...

Rx

IGOL

* Relieves constipation gently
* Increases stool bulk and maintains soft faeces
* Safest amongst all laxatives — The only laxative recommended by text books for long term use

Delicious Pineapple flavour

IGOL - for a comfortable motion every day.

Tissue effects of iron deficiency :

Glossitis occurs in 40% of patients with iron deficiency anaemia, angular stomatitis in 15% and koilonychia in 30%. Buccal mucosa shows abnormal cornification, increased mitotic figures, diminishing melanin and changes of sub-epithelial inflammation. Koilonychia may result from an abnormality of methionine or cysteine metabolism.

Patterson Kelly or Plummer Winson syndrome of sideropenic dysphagia is a well described entity. This can occur in patients of iron deficiency without anaemia. The web is found in the post- cricoid region of the hypopharynx. Sometimes there may be fibrous stricture. Histology of such webs usually shows normal epithelium but occasionally carcinoma-in-situ has been detected. Thus, this syndrome appears to be a pre-malignant condition and a close association between the syndrome and development of carcinoma has been stressed. It may be remembered that similar syndrome has been described with certain auto-immune-processes such as Sjogren's Syndrome, Hashimoto's thyroiditis and pernicious anaemia.

Stomach shows higher incidence of atrophic gastritis as well as achlorhydria. Both mucosal atrophy and achlorhydria are reversible if treated early. Children show striking mucosal changes in the small intestinal epithelium, similar to those seen in sprue.

Iron deficiency results in growth retardation and skeletal abnormalities. Children with iron deficiency tend to be significantly under-weight.

Productivity in agricultural workers has been shown to be impaired and the same improves within four days (prior to rise in haemoglobin concentration) following treatment with parenteral iron dextran. Marked behavioral changes have been shown to reverse on treatment with iron and this may be related to correction in monoamine-neuro-transmission. Some workers have suggested impaired intelligence secondary to iron deficiency. Observations regarding low scholastic achievement, low I.Q. and behavioural disturbances in iron deficient children of low socio-economic status may or may not be related to iron. Iron deficiency may induce hypothermia. This could be due to impaired conversion of T_4 to T_3.

The effect of iron deficiency on pre-disposition to infection is another long debated subject. It is known that most micro-organisms obtain soluble iron from their environment by secreting chelating agent known as sideroclones. Iron plays an important role in determining pathogenicity and virulence of infecting organisms. Transferrin deprives these organisms of iron that they require. Respiratory infections were shown to be reduced by controlling iron deficiency. Iron deficiency has been shown to reduce cellular defence mechanisms as well. There is data to suggest defective lymphocyte transformation and reduced production of macrophage migration inhibition factor (MIF) after antigenic stimulation. MIF returns of normal rapidly after iron therapy and negative Mantoux test has been shown to convert to positive. Polymorphs have been noted to have reduced

bactericidal activity in patients with latent iron deficiency. Interestingly, there is data to show increased incidence of malaria following parenteral iron therapy and one can only say that the debate on this subject has not been concluded.

IRON OVERLOAD SYNDROME

Iron overload syndrome or haemochromatosis is defined as a clinical condition where iron overload, primary or secondary (TableXII) leads to affection of various organs such as liver, pancreas, heart, endocrine glands and skin. However, recently the term has also been used to include early asympotmatic individuals who have variable degree of iron overload as depicted by laboratory tests without clinical or laboratory evidence of organ dysfunction.

Hereditary haemochromatosis (HH) is an inheritable defect of iron metabolism. Various terms like primary, familial and idiopathic suggest the same. It is transmitted as an autosomal recessive trait. It has an overwhelming incidence in males and a very high gene frequency or prevalence amongst Caucasians [66,67,68].

Secondary haemochromatosis is more commonly known as haemosiderosis. The term haemosiderosis was initially used by Finch to describe excessive haemosiderin in tissues secondary to one or other causes (Table XII). However, the term has been recently dropped as it has no specific clinical meaning. The terms like hereditary (primary) and secondary haemochromatosis are more accurate and scientific designations. We shall only consider hereditary haemochromatosis (HH) for the present review [66,67,68].

TABLE XII : CLASSIFICATION OF IRON OVERLOAD SYNDROMES (HAEMOCHROMATOSIS)

A.	Hereditary (primary or genetic) haemochromatosis.		
B.	Secondary haemochromatosis.		
	1.	i)	Alcoholic liver disease
		ii)	Postportacaval shunt.
	2.	Erythropoietic	
		i)	Haemolytic anaemia
		ii)	Refractory anaemia
		iii)	Porphyria cutanea tarda
3.	Dietary or medicinal iron excess		
4.	Hereditary atransferrinaemia		

HEREDITARY HAEMOCHROMATOSIS

Pathogenesis [69,70,71,72,73] **:**

HH has acquired a special interest now, the genetics have been well defined, its high prevalence amongst Caucasians has been realised, and benefits of early diagnosis leading to favourable prognosis have been confirmed.

However, the basic metabolic defect in HH still remains an enigma. Body iron stores are normally regulated by absorption rather than excretion. HH, no doubt, is a result of inappropriately increased iron absorption which eventually leads to extensive iron accumulation and tissue damage.

Why should excessive absorption of iron occur? Is the intestinal mucosal cell receiving an improper signal? Is the cell itself defective with respect to abnormal uptake, transport, storage or release of iron into the blood? All this remains unclear.

As against normal iron absorption of 1-1.5 mg/day, patients of HH absorb 2-6 mg of iron each day and as against storage iron of 0.5-1.0 gm, patients of HH have iron stores of 4-40 gms. This occurs in the parenchymal organs like liver, heart, pancreas andother endocrine glands leading tosignificant organ dysfunction and even death.

As against HH, in secondary Haemochromatosis (SH) iron overload is primarily in the reticulo-endothelial system (RES) and only as it increases further, it accumulates in the parenchymal cells. Majority of patients with alcoholic liver disease have subtle degree of iron overload. Those alcoholics who have severe iron overload, probably suffer from a combination of homozygous haemochromatosis and associated alcohol abuse. Various dietary deficiencies leading to ineffective erythropoiesis may also be playing some role. Occasionally, severe overload develops in alcoholic cirrhotics following an end to side portacaval shunt. The iron loading of South African Blacks (Bantu) is due to ingestion of large quantity of iron complexed with ligands generated during fermentation of alcoholic beverages which are stored in iron drums. The soluble form of iron present here, is easily absorbed. Recent studies have shown that patients in Zimbabwe get iron loaded due to drinking of traditionally made beer, secondary to the interplay between an iron loading gene which is distinct from HLA-linked gene of HH and high iron content of the beer.

Genetics [74,75,76] **:**

As stated earlier, HH is an inborn error of metabolism with an autosomal recessive inheritance. Simon in 1975 described association between HH and HLA-A3 antigen. Further reports showed association with HLA-B7. HLA-B14, and HLA-11 as well. The frequency of HLA -A3 in HH varies from 55% to 100% (mean of 73%) compared with 2-30% in controls. The gene for HH is located on the short arm of chromosome 6 and it is tightly linked to the HLA locus.

Being an autosomal recessive disorder, the homozygotes develop full clinical expression while only about 20% of heterozygotes have abnormal laboratory tests related to iron with only occasional clinical findings like arthralgia (20%), diabetes (3%) and pigmentation (2%). It is possible to identify first degree relatives at risk by family studies of the proband with HLA typing. Recently, French groups have succeeded in developing DNA probes by which it is now possible to screen homozygous siblings without HLA typing. Obviously, the disease is more frequent in siblings than offsprings, unless the homozygous-heterozygous mating occurs in the parents.

Frequency of HH [76,77,78] :

Recent studies in Caucasians from Sweden, Utah, Britain and Canada have shown carrier rate of 10% resulting in 1:150 to 1:500 homozygotes for HH. It is probable that majority of subjects of these studies were of North European descent.

Although iron is essential for the cell to function, iron overload is toxic and it causes cell death. Liver is the major site of iron storage and therefore it is particularly prone to injury. It is suggested that in patients of HH, there is increase of non-transferrin-bound-iron in the plasma which is attached to the low-molecular-weight organic molecules, possibly citrates. These complexes cannot bind to transferrin and even when transferrin is not saturated, one can detect their presence in the plasma of patients with HH. These complexes are rapidly cleared by the liver. However, at the same time they produce damage to it e.g. they catalyse free radical formation leading to lipid oxidation of organelle membranes. They also increase lysosomal fragility as well as induce collagen formation.

Clinical manifestations [79,80] :

Clinical manifestations depend on organs involved which include liver, heart, pancreas, other endocrine organs, skin and joints. The incidence varies with the stage of the disease. It is not easy to suspect HH in its initial stage as the symptoms and signs are not specific and hence a very high index of suspicion is necessary. Table XIII enlists common symptoms of HH while Table XIV gives the presenting signs.

TABLE XIII :
COMMON SYMPTOMS OF HEREDITARY HAEMOCHROMATOSIS

Arthralgia	Impotence, loss of libido, amenorrhoea
Weakness, lethargy, malaise	Pigmentation
Diabetic symptoms	Congestive heart failure : palpitation, oedema
Abdominal pain	Weight loss.

TABLE XIV :
COMMON PRESENTING SIGNS OF HEREDITARY HAEMOCHROMATOSIS

Hepatomegaly
Arthritis
Skin pigmentation, fine-wrinkled skin
Testicular atrophy
Cardiac failure and / or arrhythmias

Latent (pre-cirrhotic) stage:

Such patients are usually asymptomatic, Slight arthralgia, mild hepatomegaly and pigmentation may occur. Minor elevation in serum transaminases does occur.

Overt stage :

This includes patients of HH having one of the features enlisted in Table XIV.

Majority of clinically overt patients are males and beyond the age of 40 years. The onset and severity of clinical manifestations are influenced by age, sex, diet, blood loss, alcohol and other unknown genetic factors.

Liver disease [81,82,83] *:*

Liver involvement leads to its enlargement and subsequently cirrhosis. Patients with cirrhosis have a higher incidence of diabetes mellitus (70%), as against 20% in the non-cirrhotics. Abdominal pain and pigmentation are also common. Liver enzymes are often elevated. Hepatoma develops in 35% of patients and this is despite therapeutic phlebotomy. Hepatomas are very uncommon unless cirrhosis develops, hence the importance of early diagnosis in pre-cirrhotic stage.

Overall, patients with HH have 200 fold risk of developing a hepatoma. An Italian study has shown Hepatitis-B or Hepatitis-C positivity in two thirds of the patients with hepatoma. Patients of HH with cirrhosis have better survival than alcoholic cirrhosis. This is probably because of lower incidence of portal hypertension and oesophageal varices. Liver biopsy shows haemosiderin deposition in the hepatocytes, bile duct, epithelium and Kupffer's cells.

Cardiac manifestations [84,85,86] :

Table XV enlists the cardiac manifestations of HH. Iron is predominantly accumulated in the myocardial cells and it is more extensive in the ventricular than the atrial tissue. It also accumulates in the atrioventricular node leading to conduction defects and arrhythmias.

TABLE XV :
CLINICAL CARDIAC MANIFESTATIONS OF HAEMOCHROMATOSIS

1.	Restrictive cardiomyopathy which may mimic constrictive pericarditis.
2.	Congestive failure (biventricular, usually right)
	a) diffuse cardiac enlargement
	b) prominent neck veins
	c) hepatomegaly
	d) abdominal swelling (ascites)
	e) oedema of feet
3.	Substernal pain typical of angina pectoris
4.	Arrhythmias (atrial fibrillation, supraventricular tachycardia) .

Endocrinopathy [87,88,89,90] :

Endocrine manifestations include diabetes mellitus, hypogonadism, hypothyroidism, hypoparathyroidism and rarely panhypopituitarism and adrenal hypofunction. Diabetes mellitus (DM) is the commonest endocrinopathy with the prevalence of 40% to 80% in the full blown end stage of iron overload. However, it may be as low as 5% in patients diagnosed through pedigree studies. The pathophysiology includes pancreatic islet cell dysfunction secondary to iron deposition. Presence of cirrhosis of liver associated glucose intolerance and insulin resistance also play vital roles. Others have higher genetic predisposition as evidenced by higher frequency of diabetes in first degree relatives. Iron loading without cirrhosis also leads to insulin resistance. Thus, there are many mechanisms for development of diabetes.

Hypogonadism is common in males. It occurs in 20-75% of patients. Clinical manifestations include impotency, loss of libido and testicular atrophy. It is uncommon in females but if it occurs, it results in amenorrhoea. Its pathophysiology includes iron deposition in the hypothalamic-pituitary axis. Hence the plasma level of FSH and LH

are reduced and usually there is no response to LH releasing hormone (LHRH). Other endocrinopathies are relatively less common.

Skin pigmentation:

Over 90% of patients have generalised hyper-pigmentation which is more pronounced in the exposed areas. It mimics the appearance of suntan but occasionally, patients have a metallic grey colour. When the pigmentation is bronze, it is due to increased melanin in the epidermis, whereas the metallic grey appearance is due to combination of melanin and hemosiderin.

Arthropathy [91,92,93,94] *:*

Table **XVI** enlists the clinical features of arthropathy in haemochromatosis. This often is the presenting manifestation of HH. Obviously, it is difficult to suspect HH in patients who have no other overt manifestations. Most of the patients are misdiagnosed as osteoarthritis or as a rheumatoid variant. It often takes 10-12 years of arthropathy before haemochromatosis is diagnosed or suspected. The joints affected include small joints of the hands, wrists and subsequently even shoulders and knees. The mechanism is believed to be chondrocalcinosis (Pseudo-gout). Involvement of hip may necessitate hip replacement. Although X-rays may be normal in early cases, subsequently there is cartilage loss, cyst formation, bony overgrowth with the peculiar hook like osteophyte on the radial-side of metacarpal heads. The joint space is decreased, there is subchondral cystic erosion and even sclerosis. Linear and punctate calcification of the lateral meniscus may be visible in the knee joint films. Although the exact mechanism remains unknown, hemosiderin has been found in the synovium and the articular cartilage. Iron may inhibit pyrophosphatase activity resulting in precipitation of phyrophosphate producing chondrocalcinosis.

Abdominal pain [95] *:*

Surprisingly, abdominal pain is a frequent initial finding in patients of HH. It could be acute and severe. The common site is epigastrium and right upper quadrant. The mechanism remains unknown. It is definitely not related to cholelithiasis or peptic ulcer disease. Regular phlebotomy results in significant relief.

Uncommon manifestations [96-104] *:*

Rarely patients of HH develop hearing loss, ataxia, osteoporosis (due to lack of oestrogen or ascorbic acid), enhanced susceptibility to infection such as virbio vulnificus, yersinia enterocolitica and listeria monocytogenes. Various mechanisms have been put forward to explain these. One of them includes presence of free iron which increases virulence of the organisms. Other mechanism includes monocyte and leucocyte

dysfunction leading to reduced phagocytic and lytic activity of these cells.

TABLE XVI
CLINICAL FEATURES OF ARTHROPATHY OF HAEMOCHROMATOSIS:

*	Present in approximately 25% to 75% of patients with haemochromatosis.
*	May be one of the earliest manifestations in 30% of patients.
*	Occasionally it is the sole manifestation of haemochromatosis
*	It involves -
	Second and third metacarpophalangeal joints
	Proximal interphalangeal joints
	Knees
	First metatarsophalangeal joints
	Hips
	Wrists
	Back and neck
	Tarsometatarsal joints (rare)
	Shoulders

Diagnosis [115-118] :

Diagnosis of HH is invariably missed and made only in the advanced stage in a large number of patients. There are many reasons:-

a) lack of familiarity
b) failure to appreciate its high incidence
c) expectations regarding clinical triad of cirrhosis, diabetes mellitus and hyper-pigmentation which are all signs of advanced stage.
d) non-specificity of early symptoms.

When should HH be suspected ?

a) unexplained elevation in liver enzymes with or without hepatomegaly.
b) unexplained hepatomegaly even with normal liver function
c) diabetes mellitus with hepatomegaly.
d) arthritis affecting 2nd or 3rd metacarpophalangeal joints
e) unexplained cardiac problem
f) unexplained impotency, loss of libido, testicular atrophy or amenorrhoea.

Investigations that can lead to suspicion include :

a) high serum iron
b) increased transferrin saturation
c) increased serum ferritin.

In view of autosomal recessive inheritance, one should look for the disease in the first degree relatives of the patient, specially siblings. However this advice is usually ignored.

Assessment of iron overload includes estimating serum iron, total iron binding capacity, transferrin saturation, serum ferritin, urinary iron excretion following administration of chelating agent, bone marrow and liver biopsies for iron staining, chemical quantitation of iron in liver tissue, histopathology of liver biopsy and HLA typing. It is important to detect HH in its latent stage. Also, one has to carefully differentiate between HH and secondary iron overload syndromes.

Serum iron studies and Ferritin assay :

Transferrin saturation remains a key test in suspecting iron overload. It is more sensitive than the serum ferritin as well. Importance of ferritin lies in the fact that its elevation is proportional to the degree of iron overload, while the rise in transferrin saturation cannot be easily correlated with the quantity of tissue iron stores. Unfortunately, both transferrin saturation and serum ferritin are nonspecific and elevated in many physiological and pathological conditions. Even liver cell injury due to any reason, liberates iron and ferritin.

Chelatable iron:

High level of body iron stores (over 10 grams) nearly always result in increased iron excretion following adminstration of iron chelator e.g. desferioxamine. One cannot, however, calculate the exact total body iron stores as the degree of chelatable iron is not an entirely satisfactory test for quantitation of iron stores. In addition, this test is cumbersome and requires accurate collection of urine in iron free containers. Estimation of serum ferritin has replaced the iron chelation test.

Bone marrow iron:

Unfortunately, because of practical reasons, evaluation of marrow iron stores is of little value in the evaluation of iron overload.

Quantitation of iron in liver biopsies:

Prussian-Blue stained section of liver can be graded for its iron content by using the grading system of Scheuer and Associates. Five grades of iron deposition are described

(● to 4+). Grade 0 to 2 are considered lower normal. This system overall underestimates the storage iron. It does not measure RES iron. Grade III suggests definite increase in iron while grade IV indicates very high iron stores. However, such grading of iron is rough and semi-quantitative and hence chemical determination by the method described by Barry and Sherlock is preferred. Both colorimetric and atomic absorption spectrophotometric techniques can be used in reliable fashion.

Besides suspecting iron overload, liver biopsy gives diagnostic clues regarding its aetiology e.g. in HH, iron accumulates in the parenchymal cells with maximum deposition at the periphery of the lobules. In alcoholics, both Kupffer's cells and parenchymal cells accumulate iron.

Histopathology of the liver:

Iron accumulation in the liver leads to a characteristic pattern of fibrosis and ultimately to macronodular cirrhosis. There are no mallory bodies or liver cell swelling. Fibrosis may be minimal or even absent despite marked iron deposition.

HLA Typing :

HLA typing has helped in establishing the inheritance of HH as autosomal recessive. It has also helped in clarifying the distinction between HH and alcoholic siderosis. It helps to predict the risk of significant iron overload in siblings. Those siblings who share both the HLA haplotypes (homozygous) are at extremely high risk of developing HH. Those with one HLA haplotype, have hardly any risk of developing significant iron overload. As stated earlier, HLA-A3 is an independent marker for HH. It must be remembered that on its own, HLA typing has no value in diagnosing HH.

Computed tomography, magnetic susceptibility and magnetic resonance imaging :

Increased liver density detected on these tests correlate with liver iron and serum ferritin concentration. There are no false positive results and hence although insensitive, these tests are quite specific. These tests cannot distinguish between parenchymal and reticulo-endothelial sites of iron storage. Unfortunately, the equipment to measure magnetic susceptibility is expensive and of limited clinical application and hence unlikely to become popular.

Nuclear magnetic resonance imaging and spectroscopy have also been used with some success.

Management :

This includes phlebotomy and/or use of iron chelators.

Phlebotomy [119,120] :

Therapeutic phlebotomy is the most effective method of removing iron in HH. The goal is to produce mild iron deficiency and subsequently carry out less frequent phlebotomy to prevent reaccumulation. It is a lifelong programme. One can draw 300ml of blood once or twice a week. One should maintain the record to calculate the iron removed. Each ml of packed red cell contains 1 mg of iron and each ng of S. Ferritin equates to 10 mg of storage iron.

Haemoglobin must be determined weekly while iron studies must be performed three monthly. Once transferrin saturation is below 25% phlebotomies should be reduced to once every three weeks and after iron deficiency is induced, phlebotomies are needed once every 4-8 weeks. Occasionally, anaemia may develop before the iron stores are depleted. Hence patients must receive adequate folic acid, B_{12} , proteins and calories. High dietary iron intake should be avoided and alcohol should be discouraged.

Dietician should be consulted. Special low iron diet is not required. As many patients find lifelong phlebotomy inconvenient and expensive, one has to be very persuasive to convince them and their "Physician".

Improvement noted include decrease in pigmentation of skin, decrease in liver size, normalisation of liver enzymes, disappearance of right upper quadrant abdominal pain and improvement in cardiac failure. Arthropathy does not improve, the incidence of hepatoma does not decrease, specially if cirrhosis has already developed. Diabetes improves in 3-60% of patients. Hypogonadism does not improve.

Chelation Therapy [121,122] :

This is not needed in uncomplicated non-anaemic HH as phlebotomy is effective, cheap and safe. For patients needing blood transfusions for anaemia, chelation is a must. Desferioxamine and Deferiprone (L_1) are the only two clinically useful iron chelators. Desferioxamine is administered via subcutaneous route or intravenous infusion. This is because it has a short half life of ten minutes in plasma. Continuous 24 hour infusion gives the best results but is not required routinely. Use of portable mechanical pump is enough and additional ascorbic acid improves the iron excretion. Deferiprone (L_1) has the advantage of oral route and low cost.

Hepatic failure, diabetes and congestive cardiac failure are managed in the customary way. Arthritis would need non-steroidal anti-inflammatory agents (NSAIDs) while hypogonadism would need hormonal replacement therapy.

Prognosis [123,124] :

Therapeutic phlebotomy has effectively increased the survival rate even in cirrhotics. The five year survival is of 66% vs 18% in the untreated group. Ten years survival is 32% in the treated group and 6% in the untreated group. In non-cirrhotics, the cumulative survival rate is similar to that of a normal population. Those with cirrhosis and diabetes have worst prognosis.

Cardiac dysfunction (failure or arrhythmia) is the most frequent cause of death. Treatment does not prevent hepatoma which develops in 30% of patients after cirrhosis has developed and this is irrespective of phlebotomy. This is a major cause of death. Extra hepatic malignancies are also common.

The best prognosis occurs when the diagnosis is made in the early stage and iron overload is prevented before significant tissue damage occurs.

REFERENCES

1. `World Health Organization Technical Report Series No. 580 : Control of nutritional anaemia with special reference to iron deficiency, Report of an IAEA, USAID, WHO Joint Meeting, 1975.

2. Bothwell TH, Charlton RW, Cook JD, et al : Iron Metabolism in Man. Oxford, Blackwell, 1979.

3. Green R, Charlton RW, Seftel H, et al : Body iron excretion in man. A collaborative study. Am J Med 45:336-353, 1968.

4. Olszon E, Isaksson B, Norrby A, et al : Food iron absorption in iron deficiency. Am J Clin Nutr 31:106-111, 1978.

5. Monsen ER, Hallberg L, Layrisse M, et al : Estimation of available dietary iron. Am J Clin Nutr 31:134-141, 1978.

6. Cook JD, Monsen ER : Food iron absorption in human subjects. III. Comparison of the effect of animal proteins on non-heme iron absorption. Am J Clin Nutr 29:859-867, 1976.

7. Disler PB, Lynch SR, Charlton RW, et al : The effect of tea on iron absorption Gut 16:193-200, 1975.

8. Torrance JD, Gillooly M, Mills W, et al : Vegetable polyphenols and iron absorption. In Sultman P, Hegenauer J (eds) : Biochemistry and Physiology of Iron. New York, Elsevier, 1982, pp 819-820.

9. Cook JD, Morck TA, Skikne BS, et al : Dietary inhibitors of iron absorption in man. In Wagner PA, Kirk JR (eds) : Proceedings of the Symposium on Micronutrients in Human Nutrition. Gainesville, University of Florida, 1981, pp 99-105.

10. Cook JD, Morck TA, Lynch SR : The inhibitory effect of soy products on nonheme iron absorption in man. Am J Clin Nutr 34:2622-2629, 1981.

11. Magnusson BEO : Iron absorption after antrectomy with gastroduodenostomy. Scand J Haematol 26 (suppl) : 1-111, 1976.

12. Kuhn IN, Monsen ER, Cook JD, et al : Iron absorption in man. J Lab Clin Med 71:715-721, 1968.

13. Hall GJ, Davis AE : Inhibition of iron absorption by magnesium trisilicate. Med J Aust 2:95-96, 1969.

14. Hagermark O, Hoglund S : Iron metabolism in tetracycline-treated acne patients. Acta Dermatol (Stockh) 54:45-48, 1974.

15. Skikne BS, Lynch SR, Cook JD : Role of gastric acid in food iron absorption. Gastroenterology 81:1068-1071, 1981.

16. Beaver PC : Hemoglobin determination in hookworm disease : case findings, Am J Trop Med 31:90-97, 1951.

17. Layrisse M, Aparcedo L, Martinez-Torres C, et al : Blood loss due to infection with Trichuris trichiura. Am J Trop Med Hyg 16:613-619, 1967.

18. Farid Z, Bassily S, Schulert AR, et al : Blood loss in chronic Schistosoma mansoni infections in Egyptian farmers. Trans R Soc Trop Med Hyg 61:621-625, 1967.

19. Fairbanks VF, Beutler E : Iron deficiency. In Williams WJ, Beutler E, Erslev AJ, Rundles RW (eds) : Hematology, ed 2, New York, McGraw-Hill, 1977. pp 363-387.

20. Hoag MS, Wallerstein RO, Pollycove M : Occult blood loss in iron deficiency anemia of infancy. Pediatrics 27:199-203, 1961.

21. Calvo EB, Gnazzo N : Prevalence of iron deficiency in children aged 9-24 months from a large urban area in Argentina, Am J Clin Nutr 52:534, 1990.

22. Mills AF : Surveillance for anaemia : risk factors in patterns of milk intake. Arch Dis Child 65:426, 1990.

23. Nutrition Committee, Canadian Paediatric Society : Meeting the iron needs of infants and young children : an update. Can Med Assoc J 144:1451, 1991.

24. Agha F : Maternal foetal iron relationship. J Pakistan Med Assoc 39:281, 1989.

25. Black J : Aslan Families II : conditions that may be found in the children. Br Med J 290:830, 1985.

26. Siimes MA, Slamenpera L, Perheentupa J : Exclusive breast-feeding for 9 months: risk of iron deficiency. J Pediatr 104-196, 1984.

27. Kovar MG et al : Review of the epidemiologic evidence for an association between infant feeding and infant health. Pediatrics 74:615, 1984.

28. Godal T, Najera J : Tropical diseases 1990, Geneva, 1990, World Health Organization.

29. Weser E, Fletcher JT, Urban E : Short bowel syndrome. Gastroenterology 77:572, 1979.

30. Dunlap WM, James GW, Hume DM : Anemia and neutropenia caused by copper deficiency, Ann Intern Med 80:470, 1974.

31. Abdel-Mageed AB, Oehme FW : A review of the biochemical roles, toxicity and interactions of zinc copper and iron, Vet Hum Toxicol 32:324, 1990.

32. Philip M, Singer A, Tal A : Copper deficiency in an infant with giardiasis fed with cow's milk, Isr J Med Sci 26:289, 1990.

33. Bessman JD, Gilmer PR Jr. Gardner F : Improved classification of anemias by MCV and RDW. Am J Clin Pathol 80:322, 1983.

34. Bessman JD, Feinstein DI : Quantitative anisocytosis as a discriminant between iron deficiency and thalassemia minor. Blood 53:288, 1979.

35. Wallerstein R : Role of the laboratory in the diagnosis of anemia. JAMA 236:490, 1976.

36. Koenig H, Lightsey A, Schanberger J : The micromeasurement of free erythrocyte protoporphyrin as a means of differentiating alpha thalassemia trait from iron deficiency anemia. Pediatrics 86-539, 1975.

37. Mahu JL, Leclercq C, Suquet JP : Usefulness of red cell distribution width in association with biological parameters in an epidermiological survey of iron deficiency in children. Int J Epidemiol 19:646, 1990.

38. Bentley SA et al : The clinical utility of discriminant function for the differential diagnosis of microcytic anemias. Blood Cell 15:575, 1989.

39. Paterakis GS, Terzoglou G, Vasilioy E : The performance characteristics of an expert system for the "on-line" assessment of thalassemia trait and iron deficiency-micro hema screen. Blood Cells 15:541, 1989.

40. Green R, King R : A new red cell discriminant incorporating volume dispersion for differentiating iron deficiency anemia from thalassemia minor. Blood Cells 15:481, 1989.

41. Witte DL et al : Predicting bone marrow iron stores in anemic patients in a community hospital using ferritin and erythrocyte sedimentation rate, Am J Clin Pathol 90:85, 1988.

42. Brigden ML : The clinical utility of serum tests for iron deficiency in hospitalized patients. Am J Clin Pathol 94:245, 1990.

43. Gambino R : Misleading statement about serum ferritin. Am J Clin Pathol 94:121, 1990.

44. Plunkett J : Serum tests for diagnosis of iron deficiency. Am J Clin Pathol 94:524, 1990.

45. Guyatt GH et al : Diagnosis of iron-deficiency anemia in the elderly. Am J Med 88:205, 1990.

46. Cook JD, Skikne BS : Iron deficiency : definition and diagnosis. J Intern Med 226:349. 1989.

47. Jensen BM et al : Screening with zinc protoporphyrin for iron deficiency in non-anemic female blood donors. Clin Chem 36:846, 1990.

48. Singh T, Kochar R, Gaiha M : Estimation of marrow iron stores, biopsy vs. aspirate. J Assoc Physicians India 37:705, 1989.

49. Fairbanks VF : Laboratory testing for iron status. Hosp Pract 26(3):17, 1991.

50. Romslo I : A laboratory approach to patients with iron deficiency in general practice. Scand J Clin Lab Invest Suppl 200:55, 1990.

51. Bick RL, Baker WF Jr : Iron deficiency anemia. Lab Med 21:641, 1990.

52. Christensen D : Differentiation of iron deficiency and the anemia of chronic disease. J Fam Pract 20:35, 1985.

53. Johnson MA : Iron : nutrition monitoring and nutrition status assessment. J Nutr 120:1486, 1990.

54. Sanders WE : Diagnostic tests for iron deficiency. Ann Intern Med 75:640, 1971.

55. Jacobs A, Worwood M : Ferritin in serum : clinical and biochemical implications. N Engl J Med 292:951, 1975.

56. Beck JR : Evaluating serum tests for iron deficiency. Am J Clin Pathol 93:296, 1990.

57. Walsh JR, Fredricksen M : Serum ferritin, free erythrocyte protoporphyrin and urinary iron excretion in patients with iron disorders. Am J Med Sci 273:293, 1977.

58. Langer EE et al : Erythrocyte protoporphyrin. Blood 40:112, 1972.

59. Ratcliffe SD et al : Lead toxicity and iron deficiency in Utah migrant children. Am J Pediatr Health 79:631, 1989.

60. Cook JD : Clinical evaluation of iron deficiency. Semin Hematol 19:6, 1982.

61. Bainton DF, Finch CA : The diagnosis of iron deficiency anemia, Am J Med 37:62, 1964.

62. Bothwell TH, Charlton RW, Cook JD, Finch CA : Iron metabolism in man, Oxford, UK : Blackwell Scientific, 1979.

63. Boggs DR : Fate of a ferrous sulfate prescription. Am J Med 1987; 82:124-128.

64. Simmons WK, Cook JD, Bingham KC, et al : Evaluation of a gastric delivery system for iron supplementation in pregnancy. Am J Clin Nutr 1993; 58:622-626.

65. Auerback M, Witt D, Toler W, et al : Clinical use of the total dose intravenous infusion of iron dextran. J Lab Clin Med 1988; 111-566-570.

66. Crosby WH; Hemochromatosis : the missed diagnosis. Arch Intern Med 146:1209, 1986.

67. Finch SC, Finch CA; Idiopathic haemochromatosis : an iron storage disease, A Iron metabolism in hemochromatosis, Medicine (Baltimore) 34:381, 1955.

68. Powell LW, Halliday JW : Idiopathic haemochromatosis : In Jacobs A, Worwood M. editors: Iron in biochemistry and medicine II. New York, 1980, Academic Press.

69. Lombard M et al : Differential expression of transferrin receptor in duodenal mucosa in iron overload. Gastroenterology 98:976, 1990.

70. Cox TM, Peters TJ: In vitro studies of duodenal iron uptake in patients with primary and secondary iron storage disease. QJ Med (New Series 49) 195:249, 1980.

71. Whittaker P et al : Duodenal iron proteins in idiopathic hemochromatosis. J Clin Invest 83:261, 1989.

72. McLaren GD et al : Control of iron absorption in hemochromatosis : mucosal iron kinetics in vivo, Ann NY Acad Sci 526:185, 1988.

73. Dullmann J, Wulfhekel U : On the macrophage iron storage defect in hereditary haemochromatosis and its special importance for regulation of intestinal iron absorption. Proceedings of the Third International Conference on Haemochromatosis, Dusseldorf, Germany, July 1991 (abstract), p 5.

74. Bassett ML, Halliday JW, Powell LW : HLA typing in idiopathic hemochromatosis : distinction between homozygotes and heterozygotes with biochemical expression. Hepatology 1:120, 1981.

75. Powell LW et al : Expression of hemochromatosis in homozygous subjects : implications for early diagnosis and prevention. Gastroenterology 98:1625, 1990.

76. Borwein ST et al : Genetic and phenotypic expression of hemochromatosis in Canadians. Clin Invest Med 6:171, 1983.

77. Simon M et al : Idiopathic hemochromatosis : demonstration of recessive transmission and early detection by family HLA typing. N Engl J Med 297:1017, 1977.

78. Edwards CQ, Skolnick MH, Kushner JP : Hereditary hemochromatosis : contributions of genetic analyses. Prog Hematol 12:43, 1981.

79. Edward CQ et al : Homozygosity for hemochromatosis : clinical manifestations. Ann Intern Med 93:519, 1980.

80. Adams PC, Kertesz A, Valberg LS : Clinical presentation of hemochromatosis : a changing scene. Am J Med 90:445, 1991.

81. Niederan C et al : Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. N Engl J Med 313:1256. 1985.

82. Bradbear RA et al : Cohort study of internal malignancy in genetic hemochromatosis and other chronic nonalcoholic liver disease. J Natl Cancer Inst 75:81, 1985.

83. Fargion S et al : Analysis of risk factors for hepatocellular carcinoma in patients with genetic hemochromatosis. Proceedings of the Third International Conference of Haemochromatosis, Dusseldorf, Germany, July 1991 (abstract), p 7.

84. Swan WGA, Dewar HA : The heart in haemochromatosis. Br Heart J 14:117, 1952.

85. Bothwell TH et al : The cardiac complications of hemochromatosis. Am Heart J 43:333, 1952.

86. James TN : Pathology of the cardiac conduction system in hemochromatosis. N Engl J Med 271:92, 1964.

87. Dymock JW et al : Observations on the pathogenesis, complications and treatment of diabetes in 115 cases of haemochromatosis. Am J Med 52:203, 1972.

88. Rahier J et al : The haemochromatotic human pancreas : a quantitative immunohistochemical and ultrastructural study. Diabetologia 30:5, 1987.

89. Stremmel W et al : Abnormalities in estrogen, androgen, and insulin metabolism in idiopathic hemochromatosis. Ann NY Acad Sci 526:209, 1988.

90. Edwards CQ et al : Thyroid disease in hemochromatosis : increased incidence in homozygous men. Arch Intern Med 143:1890, 1983.

91. Schumacher HR et al : The arthropathy of hemochromatosis: recent studies. Ann NY Acad Sci 526:224, 1988.

92. Gordon DA, Little HA : The arthropathy of hemochromatosis without hemochromatosis. Arthritis Rheum 16:305, 1973.

93. Gordon DA, Clarke PV, Ogryzlo MA : The chondrocalcific arthropathy of iron overload : relationship to hemochromatosis. Arch Intern Med 134:21, 1974.

94. Schumacher HR, Jr : Hemochromatosis and arthritis. Arthritis Rheum 7:41, 1964.

95. Desforges G : Abdominal pain in hemochromatosis. N Engl J Med 241:485, 1949.

96. Neumann MA : Hemochromatosis of the central nervous system. J Neuropathol Exp Neurol 8:19, 1948.

97. Delbarre F : Les osteoporoses des hemochromatoses. Semaine Hopitaux 36:3279, 1960.

98. Delbarre F, Nobillot A : Osteoporose et hemochromatose. Int Cong Rheum Dis 2:1101, 1961.

99. Diamond T, Stiel D, Posen S : Osteoporosis in hemochromatosis iron excess, gonadal deficiency, or other factors? Ann Intern Med 110L430, 1989.

100. Capron JP et al : Spontaneous Yersinia enterocolitica peritonitis in idiopathic hemochromatosis. Gastroenterology 87:1372, 1984.

101. Chiesa C et al : Yersinia hepatic abscesses and iron overload. JAMA 257:3230, 1987.

102. Van Asbeck SB et al : Listeria monocytogenes meningitis and decreased phagocytosis with iron overload. Br Med J 284:542, 1982.

103. Koenig KL, Muoller J, Rose T : Vibrio vulnificus : Hazard on the half shell. West J Med 155:400, 1991.

104. Muench KH : Hemochromatosis and infection : alcohol and iron, oysters and sepsis. Am J Med 87:40, 1989.

105. Brissot P et al : Assessment of liver iron content in 271 patients : a reevaluation of direct and indirect methods. Gastroenterology 80:557, 1981.

106. Valberg LS et al : Diagnostic efficacy of tests for the detection of iron overload in chronic liver disease. Can Med Assoc J 119:229, 1978.

107. Worwood M : Serum ferritin. Clin Sci 70:215, 1986.

108. Barry M, Cartei G, Sherlock S : Differential ferrioxamine test in haemochromatosis and liver diseases. Gut 10:697, 1969.

109. Scheuer PJ, Williams R, Muir AR : Hepatic pathology in relative of patients with haemochromatosis. J Pathol Bacteriol 84:53, 1962.

110. Weinfeld A, Lundin P, Lundvall O : Significance for the diagnosis of iron overload of histochemical and chemical iron in the liver of control subjects. J Clin Pathol 21:35, 1968.

111. Barry M : Liver iron concentration, stainable iron, and total body storage iron, Gut 15:411, 1974.

112. Barry M, Sherlock S : Measurement of liver-iron concentration in needle-biopsy specimens. Lancet 1:100, 1971.

113. Bassett ML et al : Early detection of idiopathic haemochromatosis : relative value of serum-ferritin and HLA typing. Lancet 2:4, 1979.

114. Champman RWG et al : Computed tomography for determining liver iron content in primary haemochromatosis. Br Med J 1:440, 1980.

115. Houang MTW et al : Correlation between computed tomographic values and liver iron content in thalassaemia major with iron overload. Lancet 1:1322, 1979.

116. Howard JM et al : Diagnostic efficacy of hepatic computed tomography in the detection of body iron overload. Gastroenterology 84:209, 1983.

117. Brittenham GM, Farell DE, Harris JW : Magnetic-susceptibility measurement of human iron stores. N Engl J Med 307:1671, 1982.

118. Halliday JW et al : Serum-ferritin in diagnosis of haemochromatosis. Lancet 2:621, 1977.

119. Lufkin EG et al : Influence of phlebotomy treatment on abnormal hypothalamic-pituitary function in genetic hemochromatosis. Mayo Clin Proc 62:473, 1987.

120. Kelly TM et al : Hypogonadism in hemochromatosis : reversal with iron depletion. Ann Intern Med 101:629, 1984.

121. Modell B : Advances in the use of iron-chelating agents for the treatment of iron overload. In Brown, EB, editor : Progress in hematology, vol XI, New York, 1979, Grune & Stratton, p 267.

122. Hershko C, Pinson A, Link G : Iron chelation. Blood Rev 4:1, 1990.

123. Bomford A, Williams R : Long-term results of venesection therapy in idiopathic haemochromatosis. Q J Med 45:611, 1976.

124. Ammann RW et al : High incidence of extrahepatic carcinoma in idiopathic hemochromatosis. Scand J Gastroenterol 15(6):733, 1980.

Instant pain relief in oral distress...

Zytee

The topical analgesic, antiseptic gel.

Zytee relieves pain rapidly

Zytee reduces the risk of secondary infection

Zytee promotes faster healing

Indications : Mouth Ulcers, Gingivitis, Glossitis, Stomatitis, Denture irritation, teething trouble in infants and Cracked nipples.

Zytee

for instant relief where it hurts.

In General Debility & Loss of Appetite...

ELIXIR

Neogadine

Restores Normal Physiological Appetite

* Restores Normal Physiological Function

* Re-establishes Normal Eating Habits.

The Appetite Normaliser.

Millions of adult Indian males suffer from latent anaemia...

Their complaint : Weakness, fatigue, lack of concentration

Their need : A comprehensive haematinic

Also available as 450 ml pack

HEPATOGLOBINE

satisifies patients' therapeutic and psychological needs.

Printed by Usha Multigraphs (P) Ltd.